REMARKS/ARGUMENTS

Claims 25 and 33-37 are pending in the application. Claims 33, 34 and 35 have been amended to more clearly recite the claimed subject matter. The amendments are supported by the application as filed. Thus there is no issue of new matter. Entry of the claim amendments into the file of the present application is respectfully requested.

Amendment to the Specification

The paragraph beginning at p. 8, line 1 of the specification has been amended to delete the sentence, "*The making of these pharmaceutical preparations implies procedures in which the active ingredient is not in any case dissolved in a solvent, thus maintaining its crystalline structure.*" No new matter is added by this amendment.

Rejection Under 35 U.S.C. §101

Claims 33 and 34 are rejected under 35 U.S.C. §101. The Examiner alleges that the claims are "wholly inoperable". According to the Office Action, "*In order for the claims to be operable, the critical steps . . . must be included.*"

In response to this ground of rejection, applicants have amended claims 33 and 34 such that these claims now specifically recite subject matter deemed "critical" according to the Office Action. More particularly, the claims have been amended such that they now recite, respectively, cooling, filtering and drying steps following the heating step. As amended, the subject claims are believed to overcome the rejection under 35 U.S.C. §101. The Examiner is, therefore, respectfully requested to reconsider and withdraw the subject rejection.

Rejection Under 35 U.S.C. §112

Claim 35 is rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the 'enablement' requirement of the statute. According to the Examiner, it would require an "undue" amount of experimentation (upon consideration of the so-called "Wands factors") for one having ordinary skill in this art to form the pharmaceutical composition that is the subject of claim 35. The rejection is respectfully traversed.

Claim 35 is amended in this Response such that it now recites a solid antihistiminic pharmaceutical composition comprising the crystalline form 1 of bilastine according to claim 25 as the active ingredient together with at least one excipient.

The Examiner submits on p. 3 of the Office Action that the temperature and pressure encountered by bilastine form I (i.e., polymorph I or polymorph 1, used interchangeably) in the processing steps used in forming the claimed pharmaceutical composition recited in claim 35, would cause the 'form I' (of bilastine) to convert to one of the other polymeric forms (form 2, form 3 and/or a mixture of forms 2/3) of bilastine. The Examiner then concludes, further on p. 3 (near the bottom) that the applicants did not provide any evidence (in the specification as filed) that the crystalline drug would keep its form, i.e., that it would remain in form I in the pharmaceutical composition recited in claim 35. As indicated above the Examiner's ground of rejection is respectfully traversed in that applicants contend that one having an ordinary degree of skill in this art would find that the teachings contained in the application as presently filed without question do enable the formation of a solid pharmaceutical composition as presently recited in (amended) claim 35, which formation would not require any undue experimentation to prepare.

Provided with this Response is a Declaration Under 37 C.F.R. §1.132 of Maria Luisa Lucero de Pablo, who is a co-inventor of the present application and an employee of Faes Farma, S.A., the owner by Assignment of the invention and the application. The declaration contains evidence to support applicants' contention herein that teachings contained in the application as originally filed do enable one having an ordinary level of skill in the related art to prepare a solid antihistiminic pharmaceutical composition, i.e., as presently recited in claim 35, without the need for any undue experimentation in doing so.

Paragraph 5 states, with reference to the teachings contained in the application as filed, that form I of bilastine has the greatest stability, i.e., as compared to forms II and III. This holds true even when the bilastine is stored at room temperature and above. Further, during the formation of form I of bilastine from polymorphs II and III, no conversion of the form I thus formed into either of the other two forms is encountered, notwithstanding the temperatures and pressures encountered during the process of formation.

Paragraphs 7, *et seq.* of the attached 1.132 declaration detail the results achieved with a series of experiments carried out by, or under the direction and control, of the declarant for the purpose of demonstrating the stability of bilastine form 1 during the process of producing a solid pharmaceutical formulation, i.e., in accordance with claim 35. In paragraph 8, for instance, the declarant discusses the effects observed with combining form 1 of bilastine with a variety of excipients as analyzed with the use of a Differential Scanning Calorimetry ("DSC") technique. The study included combining bilastine form I with excipients commonly encountered in solid dosage formulation, including those found in a 'typical' tablet formulation, i.e., useful in forming the composition recited in claim 35. The results of this testing, which support applicants' position, are set forth in Table 1 appended to the declaration.

Next, as described in declaration paragraph 9, a preformulation study was conducted of an immediate-release tablet formulation. This formulation also would fall within the scope of the solid pharmaceutical composition recited in claim 35. As stated in paragraph 9, "The results obtained clearly demonstrate that variability in the crystalline form between the various batches is very low and acceptable." (emphasis supplied).

As further detailed in paragraph 10 of the declaration, as shown in the data in Tables 3 and 4 provided with the declaration, a mixture of polymorphs II and III is chemically and thermically unstable after 15 days of irradiation by visible A and B light whereas, in contrast, crystalline form I is stable after being irradiated in the same manner for up to 30 days. Further, in a photostability study of bilastine form I, no significant degradation impurities or changes in Differential Scanning Calorimetry (DSC) results were observed with the material placed in transparent glass containers, amber glass containers and even when directly exposed to the light.

Still further, according to paragraph 11 of the declaration, data obtained under stress conditions (see Tables 5 and 6 provided as attachments to the declaration) clearly demonstrate that polymorphic form I is completely stable against temperature and humidity in multiple stability studies, whereas mixtures of polymorphs II and III demonstrate a degree of hygroscopicity which complicates the process of pharmaceutical formulation.

Based on the evidence provided in the declaration, the co-inventor/declarant was able to conclude that polymorph form I of bilastine demonstrates remarkable stability and would not convert to another form (i.e., form II, form III or form II/III) due to the temperature and/or pressure encountered during formulation of a pharmaceutical composition according to claim 35.

Thus, the teachings contained in the specification of the application as originally filed are deemed by applicants to completely enable the subject matter recited in claim 35. For all of the reasons presented herein, therefore, the Examiner is respectfully requested to reconsider and withdraw the 35 U.S.C. 112, paragraph 1 "enablement" rejection of applicants' claim 35.

Rejection Under 35 U.S.C. §§102/103

In paragraph 4 of the Office Action claims 35-37 are rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Orjales, et al. U.S. Patent No. 5,877,187, or alternatively, under 35 U.S.C. 103 as being allegedly 'obvious' over Orjales, et al. in view of Rowland and Tozer supplemented with Corcostegui, et al. The rejection is respectfully traversed.

Amended claim 35 defines a solid pharmaceutical formulation of polymorph 1 of bilastine which is clearly not taught or even suggested by Orjales et al., or in any of the other cited references for that matter. As noted above, bilastine keeps its crystalline form 1 during processing to solid pharmaceutical preparations and such preparations are stable during storage. Therefore, the process for treating allergic diseases comprising administering to a patient an effective amount of crystalline form 1 of bilastine or a pharmaceutical composition thereof, as recited in claims 36 and 37 are also novel and unobvious over the cited references.

With regard to the obviousness rejection, applicants note that some organic compounds can present a single crystalline form while other compounds present several polymorphic structures and it is not possible to predict either the number of crystalline modifications nor their physico-chemical properties. The solid-state form of the active substance can drastically alter the properties of a pharmaceutical product. It may change the effectiveness, stability and suitability of a particular formulation. Therefore, developing the most adequate solid form is critical for the success of a product and it is therefore not an obvious matter.

Orjales et al. does not mention that the existing forms of bilastine (i.e. forms 2 and 3) are not sufficiently stable and does not even teach that more than one crystalline form of bilastine could exist. Therefore, there is no incentive in the references combined with Orjales et al. which would have prompted the skilled person to try finding a new crystalline form of bilastine and no indication that such form would exist and would additionally show an improved stability.

Consequently, claims 35-37 are submitted as being novel and non-obviousness over the cited prior art. Thus the rejections of the subject claims based on §§102/103 should be withdrawn.

Respectfully submitted,

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